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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/602,441	06/24/2003	Anish Sen Majumdar	086/002	5072

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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	PAPER NUMBER
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/602,441	MAJUMDAR ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 9-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 9-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/26/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed December 6, 2006 has been received and entered. Applicants have amended claims 1-6, 9 and 10, while claims 7-8, 13-24 has been canceled.

Election/Restrictions

Applicant's election without traverse of the invention of group II (claims 13-24, nucleic acid composition) filed April 13, 2006 was acknowledged. However, Applicants traversed the requirement of election between composition and method and therefore, these groups were rejoined for examination purposes. Applicants' argument of examining method for eliciting an immune response with the elected group comprising plurality of polynucleotide composition was found persuasive. Applicant's also traverse the requirement of election of one TERT sequence. Applicant's argument of examining other sequences with elected Sequence ID 4 was found not persuasive, as each of these sequences have distinct structure as stated in previous office action. Applicants also elected GM-CSF as specie for immunization promoting factor.

Claims 1-6 and 9-12 are under consideration.

Withdrawn-Claim Objections

The objection to claims 1-24 is withdrawn in view of amendments to the pending claims.

New Grounds of rejection-Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 and 9-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for eliciting an immune response in a mouse that is specific for its own telomerase reverse transcriptase (TERT), comprising administering an immunogenic composition comprising a nucleic acid encoding a protein with at least 20 consecutive amino acids of TERT of another mammalian species by intramuscular or intra dermal injection to the mouse does not reasonably provide enablement for a method for eliciting an immune response in a human to hTERT by administering to the human an immunogenic composition containing a nucleic acid encoding TERT of a nonhuman mammalian species intended to generate anti cancer effect. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a

determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on factors discussed in MPEP 2164.01(a) and the evidence as whole, it is not necessary to discuss each factor in written enablement rejection." These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

As amended claim 1 is directed to a method for eliciting an immune response in human that is specific for its own TERT by administering to the subject an immunogenic composition containing a nucleic acid encoding a protein with at least 20 consecutive amino acids of TERT of a nonhuman mammalian species. Claim 2 limits the protein of method of claim 1 to include at least 100 consecutive amino acids of TERT of the other mammalian species. Claim 3 limits the method of claim 1 to include administering the nucleic acid to at least four different occasions. Claim 4 id directed to method of claim 1 to further comprise a subsequent administration of a second composition containing a

second nucleic acid encoding protein with at least 20 consecutive amino acids of human TERT. Claim 5 limits the immune response to include a cytotoxic T cell response. Claim 6 limits the protein of claim 1 to include full-length TERT. Claim 9 limits the composition in method of claim 1 to include either plurality of nucleic acids encoding plurality of different proteins, each comprising at least 20 consecutive amino acids of TERT from one or more mammalian species different from the mammalian subject to which the composition is administered. Claims 10-11 limit the protein of claim 1 to SEQ. ID NOs: 4 the composition containing an adenovirus expression vector encoding the protein. Claim 12 includes a factor selected from IL-12, GM-CSF, IL-2 and MPL in the composition of claim 1.

The aspects considered broad are: eliciting an immune response in human by administering DNA vaccine in any form (naked DNA as well as in expression vector) administered via any route with or without GM-CSF or other adjuvant intended to generate anti-cancer effect.

In the instant case, a broadest reasonable interpretation of pending claims in view of teaching in the specification embrace a method of eliciting immune response to hTERT are intended to generate anti-cancer response in humans (see para. 54-59 of the published application and Figure 8). The specification fails to provide an enabling disclosure commensurate with full scope for the claimed invention because it fails to provide sufficient guidance as to (i) how an artisan of skill would have practiced the claimed method in eliciting an immune response by administering a nucleic acid encoding a TERT protein delivered via any route and site subsequently limiting to

administration of any expression vector encoding TERT protein, (ii) the claimed method would have resulted in an immune response in human intended to generate anti cancer response. An artisan would have to carry out extensive experimentation to make and use the invention, and such experimentation would have been undue because method to elicit an immune response in a human by delivering DNA vaccine is unpredictable and inefficient and specification fails to provide any specific guidance as to how the claimed method would have been practiced in humans. As will be shown below, these broad aspects were not enabled commensurate with the full scope for the claimed invention at the time of filing of this application because neither the specification nor the art of record taught sufficient guidance to practice the claimed invention. For purposes to be shown in the state of the prior art, the question of lack of enablement is discussed.

Claims 1-6, 9-10 embrace a method for eliciting an immune response in a human that is specific for its own TERT by administering to the human an immunogenic composition containing a nucleic acid encoding a protein with at least 20 consecutive amino acids of TERT of nonhuman mammalian species. The specification has exemplified a vaccination with human TERT expression vectors to impart a response that is cross-reactive to epitopes on mouse TERT. The specification uses a mouse model wherein mice are immunized intramuscularly with hTERT. The results of cytotoxic T cell mediated target killing shows that immunization with hTERT generates CTLs that is specific for the mouse TERT expressed endogenously by the B16F10 tumor (see example and Figure 3). The specification also discloses that the combination human and mouse TERT DNA vaccination showed a better response than mouse

TERT DNA alone in generating mTERT- specific CD8 positive CTL response that was enough to regress the growth of mouse tumor cells (see Figure 5). In a post filing art, den Hurk et al (Immunol Rev. 2004; 199:113-25) emphasizes that the concept of DNA immunization has proven to be extremely successful in inducing immune responses in mice, however, significant barriers exist to effective induction of immunity in large animals and humans using DNA immunization. den Hurk et al states "Indeed, there is not one DNA vaccine that has been approved for either human or veterinary use. This lack is mainly due to their relatively low efficacy, specifically in target species (emphasis added) (see page 114, col. 1, last para.). den Hurk et al also desribes that chemokines have also been incorporated into DNA vaccines for mice, these compounds have not been reported in target speestablishes any nexus between the effect seen in mice extrapolated to human. In fact, most of the prior and post filing art teach difficulty in achieving effective induction of immunity in large animals and humans as supported by the art of record (supra). Furthermore, claim 12 limits the method of claim 1 to plurality of cytokine as adjuvant to enhance immune response. However, it is noted that den Hurk while describing the role of adjuvants in DVA vaccination states variable immune rsponse in different species depnding on route and site of adminstration. den Hurk descibes "plasmid encoding gB and gD from PRV that are administered intramuscularly together with various combinations of the cytokine constructs along with GM-CSF show enhanced immune response and protection against virus, while the IL-2 and IFN-γ constructs had no adjuvant effects". Contrary to this in an another study, co-administration of a plasmid encoding GM-CSF showed no significantly change the

antibody or T-cell response in an immunized pigs (see page 116, col. 2). Furthermore, den Hurk et al emphasize that the timing of delivery and the dose of the plasmid encoding the cytokine may be critical, and those issues have rarely been addressed (see page 119, col. 1, para 2). Thus, it is clear that a enhancement in immune response showed varying imuune response in different species with different adjuvant even after filing of instant application. The specification does not provide any specific guidance to indicate that administration of nucleic acid encoding TERT along with any of the adjuvant descibed in the specificaton would specifically show contemplate biological activity in humans. In adsence of evidence to the contrary, it is not clear that these elements would be functional in human or in a comparable larger animal model in the same manner as they have been demonstrated in the mice. Thus, the art of record at the time of the invention does not provide enabling support for the claimed invention of eliciting immune response by delivering xenogenic nucleic acid encoding non-mammalian TERT. An artisan would have to perform undue experimentation to empirically test different routes and adjuvant to determine if xenogenic DNA would elicit an immune response in human or any other comparable larger mammal as broadly recited in the instant claims.

Claims 1-6 and 9-12 are directed to a method for eliciting an immune response in a human to hTERT by administering to the human an xenogenic composition containing a nucleic acid encoding a protein with at least 20 consecutive amino acid of TERT of nonhuman mammalian species. It is noted that claims 1-6 and 9-10 read on administering naked DNA without any adjuvant to elicit immune response in human.

Subsequent claim 12 includes GM-CSF in the immunogenic composition of claim 1. However, at the time of filing of this application, Rosenberg et al (Hum Gene Ther. 2003 20; 14(8): 709-14) states "immunization with plasmid DNA represents a theoretically attractive method for increasing T cell responses against cancer antigens". Rosenberg et al show administration of plasmid DNA encoding the gp100 melanoma-melanocyte differentiation antigen to 22 patients with metastatic melanoma demonstrated no significant clinical or immunologic responses to plasmid DNA encoding the "self" nonmutated gp100 tumor antigen" (See abstract). It is noted that contrary to effect seen in experimental animals, Rosenberg concludes that neither intramuscular nor intradermal injection of DNA encoding the gp100 nonmutated melanoma-melanocyte antigen was capable of raising cellular immune reactivity or a significant incidence of anti tumor effects in patients with metastatic melanoma (see page 713, co. 2, last para. and references of den Hurk, supra). The specification does not provide any specific guidance to overcome this art-recognized unpredictability that immune response seen in smaller experimental animal could be extrapolated to immune response at same levels in humans. The art of record teaches difficultly in achieving any significant immune response in human upon administration of a plasmid or DNA vaccine. Furthermore, amended claims 1-6, 9-12 read on administering nucleic acid encoding a TERT protein of a nonhuman mammalian species via any route to any site of the human. In additon, the scope of invention as claimed encompasses administering the immunogenic composition of the invention via any or all route of administration (i.e oral, intranasal, intramuscular, intravenous, subcutaneous etc.). It has been difficult to predict the

efficacy and outcome of transduced naked DNA or adeno viral vector encoding the protein because several factors influence the resulting immune response. The transduction of target cells, type of target cells and choice and/or characteristics of delivery vectors, route and site of delivery are some of the important determinant that influence the immune response upon administration of any DNA based vaccine. Prior to instant invention, McCluskie teaches that route of delivery of DNA vaccine influences immune responses in laboratory animals (McCluskie et al 1999 Mol. Med. 5:287-300; Abstract). Specifically, in one study McCluskie et al observed lack of response to non-injected routes of administration of DNA based vaccines, such as oral routes, sub lingual, inhalation and vaginal wall due to variation in transfection efficiency (Abstract). Prior to instant invention Scheerlinck et al (Vaccine. 2001 Mar 21;19(17-19):2647-56) emphasize the importance of route of immunization which is critical determinant of immunogenicity. Scheerlinck et al describes that "intramuscular injection of DNA vaccines results in the production of only very small amounts of protein Ag. Since the amounts draining to the local lymph nodes would be even smaller, improving the transport and/or retention of Ag in the draining lymph node could improve immunogenicity of the Ag (see page 2652, col. 1, last para.). Scheerlinck et al also describe that the route of immunization influenced the effect of genetic adjuvants. The observed differences in the effect of genetic adjuvants with the route of immunization may reflect the fact that these adjuvants require interactions with cells present at one tissue site but not necessarily at another site (see para 2653, col. 2, last para). The specification and prior art do not teach a method for eliciting immune response in

human to hTERT by administering the nucleic acid based immunogenic composition by delivering via any route such that it elicit a immune response for a sustained duration intended to generate anti cancer effect. Given the lack of guidance provided by the specification, one of skill in the art would be left to speculate as to the conditions and/or steps necessary for eliciting an immune response in human. It would have required undue experimentation for one of skill in the art to make and use the invention as claimed without a reasonable expectation of success.

In conclusion, in view of breadth of the claims and absence of a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled for the claimed inventions commensurate with the full scope of the claims. The specification and prior art do not teach a method of eliciting immune response in humans by *in vivo* delivery of DNA vaccine. An artisan of skill would require undue experimentation to practice invention commensurate with full scope because the art of DNA vaccine and *in vivo* delivery to elicit an immune response in human intended to generate anti cancer response in general by recombinant vaccine containing xenogeneic sequence of TERT was unpredictable at the time of filing of this application as supported by the observations in the art record.

Withdrawn-Claim Rejections - 35 USC § 102

Claims 13-21 and 23-24 rejected under 35 U.S.C. 102(b) as being anticipated by Morin et al (WO 99/27113, dated 6/3/1999, IDS) is withdrawn in view of cancellation of claim 13-21 and 23-24.

Withdrawn-Claim Rejections - 35 USC § 103

Claims 13 and 22-24 rejected under 35 U.S.C. 103(a) as being unpatentable over Morin et al (WO 99/27113, dated 6/3/1999, IDS) and Chen et al (US Patent publication number 20030143228, dated 7/31/2003, effective filing date 10/29/2001) is withdrawn in view of cancellation of claim 13-21 and 23-24.

Claims 1-13 and 19 rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al (US Patent publication number 20030143228, dated 7/31/2003, effective filing date 10/29/2001), and Morin et al (WO 99/27113, dated 6/3/1999, IDS) and further in view of Tian et al (Progress in Natural Science, 2001, 11(12), pp 893-904) is withdrawn in view of amendments. Furthermore, none of the cited reference explicitly provides motivation to adminster xenogenic sequence of TERT to elicit immune response in human.

Conclusion

No Claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Chen et al (US Patent publication number 20030143228, dated 7/31/2003, effective filing date 10/29/2001), Morin et al (WO 99/27113, dated 6/3/1999, IDS), Tian et al (Progress in Natural Science, 2001, 11(12), pp 893-904), Stetiz et al (Int. J Cancer, 2000, 86, 89-94), Wolchok JD (Amn. Society Gene Therapy Meeting, Abstract 218, Boston, MA, 2002, IDS) and Ferrone te al (Amn. Society Gene Therapy Meeting, Abstract 102, Boston, MA, 2002, IDS). It is noted that combination of these references could be applied in response to amendment to the claims for eliciting immune response in experimental animal using xenogenic sequence of TERT.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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